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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
EINSMANN, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/761,579	Applicant(s) SMITH ET AL.	
	Examiner Juliet C Einsmann	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/13/02; 7/9/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *3-7,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-3 in Paper No. 9 without traverse is acknowledged. Applicant's further election of the single polymorphism at position 1388 of SEQ ID NO: 2, with traverse in paper number 14 is also acknowledged. The traversal is on the ground(s) that claim 1 covers a method of diagnosis involving determining the sequence at one, two or three of the specified positions that if the restriction requirement is allowed to stand it will limit applicants to claiming methods for determining the sequence at only one of the positions. This is not persuasive, nor is it necessarily accurate. Claims which particularly require the examination of more than one polymorphic site were not presented. The claims, as presented and restricted, only **require** the determination of the sequence at a single polymorphic site. The restriction requirement was based on the claim set as presented, not a hypothetical claim set. Thus, since the claims require only the sequencing of a single position, and all three of the recited positions are independent and distinct from one another and the search and examination of all three separately would pose a significant burden to the examiner, the requirement that applicant select a single polymorphism for examination is proper. The requirement is therefore made FINAL.

2. Claim 8 is hereby rejoined to group I, as per a discussion with Janis Fraser on 9/24/02 and is examined herein. Claims 1-10 are pending. Claims 3-7 and claims 9-10 are withdrawn as being drawn to non-elected groups. Claim 3, although designated as part of elected group I is non-elected because it requires only the detection of the two non-elected polymorphisms.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Detection of Polymorphisms in the Human Pyruvate Dehydrogenase Complex E1α Gene.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 2, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are indefinite over the recitation "determining the sequence of the nucleic acid of the human at position..." and claim 8 is indefinite over the recitation "determining the sequence of the nucleic acid at one or more of position..." because it is unclear how you determine a sequence at a single position of a nucleic acid. The word "sequence" implies the determination of the nucleotide present at more than one position of a nucleic acid, yet the claims set forth that the sequence is determined at one or more of the recited positions. It is not clear how a sequence can be determined at a particular position. Amendment of the claim to recite, for example, "determination of the nucleotide present at position 1388 of SEQ ID NO: 2" would obviate this rejection.

Claims 1, 2, and 8 are further indefinite over the recitation "determining the status of the human by reference to polymorphism" because it is not clear what this step is requiring. It is not clear what it means to determine the status of a human "by reference to polymorphism."

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting and sequencing the human pyruvate dehydrogenase complex E1α (PDH E1α) gene and portions thereof, does not reasonably provide enablement for methods which are limited to the detection of a polymorphism at position 1388 of SEQ ID NO: 1. Furthermore, the specification does not provide enablement for methods in which a polymorphism is diagnosed and then a PDH drug is administered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection applies to the instant claims insofar as they might be interpreted as methods for the detection of the presence or absence of particular single nucleotide polymorphisms. It applies to claim 8 insofar as the claim implies that there would be a connection between the step of detection of the polymorphism and the administration of the PDH drug. Insofar as the instant claims read generally on methods for sequencing the human pyruvate dehydrogenase complex E1α (PDH E1α) gene, this rejection does not apply. The teachings of the specification (at, e.g., page19) and of the prior art as exemplified by Koike et al. disclose

methods of detecting and sequencing the PDH E1α gene and portions thereof. Such methods are encompassed by the instant claims as written, and a person skilled in the art could clearly practice methods of detecting and sequencing a known gene without further guidance. However, it is unpredictable as to whether one of skill in the art could use without undue experimentation methods requiring detection of the polymorphism at position 1388 of SEQ ID NO: 2 or methods for treatment which comprise detection of the polymorphism at position 1388 of SEQ ID NO: 2, which methods are also encompassed by the claims.

It is noted that the instant claims each recite methods which comprise the detection of nucleotide sequences at one or more of three different polymorphic sites. A restriction requirement was set forth in which applicant was required to select a single polymorphic site for examination. Applicant selected the polymorphism at position 1388 of SEQ ID NO: 2. This enablement rejection considers only this site in the claim.

The instant claims are drawn to methods for the diagnosis of a polymorphism in an PDH E1α gene in a human. The methods comprise steps in which the particular nucleotide present is detected at a particular position in SEQ ID NO: 2. Claim 8 further comprises a step in which a PDH drug is administered in an "effective amount."

The specification teaches that the genetic abnormalities in the PDH complex are the most common cause of primary lactic acidosis in humans, and that the majority of cases have been linked with a defect in PDH E1α subunit (page 2), and that the activity of PDH is reduced in diabetic patients. Further, the specification provides three polymorphisms in the PDH E1α gene. In particular, the specification teaches a polymorphic site at position 1388 of SEQ ID NO: 2, in the 3' untranslated region of the PDH E1α gene. The specification is silent with respect to the

effect of this polymorphism on the biological activity of the PDH E1α gene. The specification does not disclose any relationship between the presence of this polymorphism a change in the activity or expression of the PDH E1α subunit or between the presence of a particular allele of this polymorphism and any particular disease state or physiological condition.

The prior art provides polymorphisms in the coding portion of the PDH E1α gene. For example, Dahl et al. (Human Mutation, 1 :97-102 (1992)), provides a summary of known PDH E1α mutations (Table 1). These mutations are all within the coding sequence of the PDH E1α gene, and they all result in changes to the encoded polypeptide. The prior art is silent with regard to any polymorphisms in the 3' untranslated region of the PDH E1α gene. The prior art does not provide specific guidance with regard to the polymorphism identified herein as being at position 1388 of SEQ ID NO: 2.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis)

it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different polymorphisms in the PDH E1α gene, it remains highly unpredictable as to the biological significance of these polymorphisms, particularly the elected polymorphism which is outside of the coding region and has no apparent effect on the encoded gene. Thus, the claimed method directed towards the diagnosis of polymorphisms, or treatment of disease following diagnosis of polymorphisms, for enablement of the full scope, requires the knowledge of unpredictable and potentially non-existent associations between the instantly elected polymorphism and some phenotypic trait. Even if the elected polymorphism is in some way associated with some disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a

higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the PDH E1α gene prior to treatment with a PDH E1α drug.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. With regard to claims directed towards simple detecting the presence of the gene polymorphism, applicant speculates that these polymorphisms "may help to identify patients most suited to therapy with particular pharmaceutical agents (specification, page 3)." However, since the effects of any given polymorphism on gene activity are highly unpredictable, it is impossible to predict from the teachings of the instant specification what identifications can be made using the instantly claimed methods. That is, the specification does not provide any guidance as to how the polymorphism at position 1388 of SEQ ID NO: 2 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. Furthermore, with regard to claim 8, which recites a method of treatment of a PDH E1α disease, the specification does not provide any guidance as to what disease is in fact associated with the presence or absence of the polymorphism at position 1388 of SEQ ID NO: 2, other than the suggestion that these methods could be carried out for "PDH E1α mediated diseases." The specification further fails to provide any guidance as to the appropriated PDH E1α drug to be administered after the detection of the polymorphism, or the desired effect of administration of the drug (i.e. to up or down regulate the activity of the gene, and how either of these is to be accomplished). The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any disease in

particular, or for disease in general, or how to use the disclosed polymorphism to select a proper course of treatment of a disease.

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention, one would have to establish a relationship between the polymorphism at nucleotide 1388 of SEQ ID NO: 2 some physiological or disease state or some disease treatment method. Indeed, even to use the method of claim 1 to identify patients suited for particular pharmaceutical agents, one would need to know that the polymorphism at nucleotide 1388 of SEQ ID NO: 2 was in some way associated with response to some pharmaceutical agent. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the C/T polymorphism at position 1388 and any disease or condition. Further, absent a teaching the C/T polymorphism at position 1388 is not associated with such conditions, it is further unpredictable as to whether detection of the C/T polymorphism at position 1388 would be useful in predicting, e.g., the absence or decreased likelihood of such conditions.

Furthermore, it is noted that the practice of the invention of claim 8 requires the administration of a PDH E1α drug. The specification describes such a drug as being any drug which changes the level of PDH E1α or activity of PDH E1α (p. 4), but the specification fails to provide any such drugs. The specification on page 14 prophetically discusses drugs which increase PDH E1α activity, but again, fails to provide any such drugs, or to disclose a relationship between treatment with these drugs and the polymorphism at position 1388 of SEQ ID NO: 2. The identification of such drugs and/or a relationship between and the elected polymorphism would be highly unpredictable, requiring an extensive amount of research and experimentation.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is concluded that undue experimentation would be required to use the instantly claimed invention. Thus, with respect to claims 1-2, although the specification certainly enables one to detect the presence of the polymorphism (i.e. the "make" portion of 112 1st paragraph), it would require undue experimentation in order to determine how to use the methods of claims 1-2. Considering all of the factors discussed herein, it is concluded that it would require undue experimentation to determine the particular disease state that can be diagnosed and treated and thus to practice the claimed invention commensurate in scope with the present claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Koike et al. (Gene 93 (1990) 307-311).

Koike et al. teach a method for the diagnosis of a polymorphism in an PDH E1α gene in a human which comprises determining the sequence of the nucleic acid of the human at position 1388 of SEQ ID NO: 2, and determining the status of the human by reference to polymorphism in the PDH E1α gene (p. 310 and FIG. 1). Specifically, Koike et al. teach a method for sequencing the PDH E1α gene (p. 310). At least nucleotides Nucleotides 15974-16246 of the sequence taught by Koike et al. are identical to nucleotides 1200-1472 of instant SEQ ID NO: 2, thus encompassing the position 1388 of SEQ ID NO: 2. This reference is considered to teach the invention of claims 1 and 2 because the method contains only two method steps, one in which the sequence at position 1388 of SEQ ID NO: 2 is determined (i.e. which is inherently accomplished by sequencing the portion of the gene that overlaps with position 1388 of SEQ ID NO: 2), and one in which the "status of the human by reference to polymorphism" is determined. Determining the sequence of the gene is considered to inherently determine the status of the human by reference to the polymorphism because by sequencing the nucleotide present at position 1388, the status of the polymorphism is determined.

Conclusion

10. No claims are allowed.

11. A rejection for lack of utility under 101 has not been applied to claims 1-2 because these claims encompass an embodiment that would have utility, namely the sequencing of the PDH E1α gene, which itself is known to be associated with physiological and disease states (see specification, page 1). If the claims are narrowed to exclude this embodiment, these claims may be subject to such rejections.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

W. Gary Jones
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Juliet C Einsmann
Examiner
Art Unit 163434

October 17, 2002